REMARKS

Claims 1, 4, 5, 8-23 and 26-32 were pending prior to this Response. By the present communication, no claims have been added or canceled, and claims 1 and 32 have been amended to correct typographical errors. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Accordingly, claims 1, 4, 5, 8-23 and 26-32 are currently pending in this application.

Rejection of under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8, 19-27 and 29-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers et al. (hereinafter "Sommers") in view of Herrick-Davis et al. (hereinafter "Herrick-Davis").

The Examiner maintains that Sommers teach a method for identifying consitutively activating mutations by making a library carrying random as well as site directed mutagenesis to substitute the amino terminus and transmembrane regions of the STE2 gene in yeast. Applicants' respectfully disagree with the Examiner's interpretation of the response filed November 18, 2005. Specifically, Applicants *do not* "argue that Sommers et al teach random and site directed mutagenesis...," as indicated in the Advisory Action on page 2. The response filed on November 18, 2005, indicated that "*The Examiner* relies upon Sommers for disclosure of random as well as site directed mutagenesis...." (Response to Final Office Action, page 7, emphasis added).

Applicants maintain that Sommers does not teach providing a library of coding sequences for potentially activating mutations of a candidate receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Sommers discloses screening a library of *random* mutations to the amino terminus and transmembrane regions of the STE2 gene in yeast. Then, "[m]utations identified by screening of the PCR-generated libraries *were recreated* by site-directed mutagenesis to separate the multiple substitutions that were present in most alleles and to confirm that the identified sequence alterations were responsible for the altered phenotype." (Sommers, p. 6901, col. 2, first paragraph, emphasis added). Sommers further indicates that "[they]

would not expect to recover any of the additional site-directed mutants created by ... [other researchers], as they are detected only in supersensitive sst2- strains or they require multiple base substitutions, which would be rare in random mutational libraries." (Sommers, p. 6907, col. 1, lines 4-8). Thus, in order to generate a library of site-directed mutants, Sommers must first identify which mutations are of interest by screening a library of random mutants. Without first screening the library of random mutants, Sommers would not have known which substitutions are worthy of being re-created. Accordingly, the mutations of Sommers are initially identified and selected from a random library, while the mutations of the current invention are identified directly from a library of site directed mutations.

Applicants maintain that the disclosure of Herrick-Davis does not cure the above-described deficiencies in Sommers for teaching or suggesting the claimed invention. Herrick-Davis allegedly discloses application of site directed mutagenesis to substitute amino acids with longer side chains or of different polarity with aromatic substitutions. Specifically, Herrick-Davis discloses that mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT_2c receptor activates the receptor. The library is expressed in a mammalian host cell. However, according to the Examiner, Herrick-Davis does "not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene." (Office Action dated December 15, 2004, page 8). In addition, Herrick-Davis specifically states that "the increases in agonist binding affinity and potency at the mutant receptors did not result from increased receptor expression but are *directly related to the substitutions made at amino acid no. 312.*" (Herrick-Davis, page 1141, col. 1, lines 1-5, emphasis added). Further, "[a]dditional studies were performed to determine if agonists other than 5-HT display an increased affinity for S312K receptors." (Herrick-Davis, page 1140, col. 2, first paragraph). Herrick-Davis does not disclose, nor even suggest substitution of amino acids other than no. 312.

Applicants respectfully submit that one of skill in the art at the time the invention was made would not have found it prima facie obvious to combine the disclosures of Sommers and Herrick-

Davis to arrive at Applicants' invention. Even if one were motivated to combine Sommers with Herrick-Davis, Applicants submit that the proposed combination would teach away from creating a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids because (1) Sommers initially screens a library of random mutations to select substitutions of interest, which are then re-created by site-directed mutagenesis; (2) Sommers' substitutions are not limited to those required by Applicants' invention; (3) Herrick-Davis does not disclose or suggest the library of coding sequences as required by Applicants' invention; and (4) Herrick-Davis focuses solely on amino acid no. 312 of the receptor, rather than replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids. Accordingly, for the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 9-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers in view of Herrick-Davis and further in view of Barak, et al. (hereinafter "Barak"). The remarks above distinguishing the invention over the disclosures of Sommers and Herrick-Davis apply equally here. Barak allegedly discloses using a heterologous reporter system where the reporter gene green fluorescent protein is made in fusion with beta arrestin under mammalian promoter control, and is expressed in cells such as insect cells, plant or animal cells including, but not limited to, HEK cells, HeLa cells, COS cells and primary cells. However, Barak is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Barak with Sommers and Herrick-Davis to arrive at the claimed invention. Even if one were motivated to combine Barak with Sommers and Herrick-Davis, Applicants submit that the proposed combination would not yield the claimed invention because Barak merely provides a reporter gene for use in detection assays, and is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sommers in view of Herrick-Davis and Barak, further in view of Lerner, et al. (hereinafter "Lerner"). The remarks above distinguishing the invention over the disclosures of Sommers, Herrick-Davis and Barak apply equally here. Lerner allegedly discloses identifying antagonists or agonists for G-protein coupled receptor using a pigment cell. However, Lerner is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Lerner with Sommers, Herrick-Davis and Barak to arrive at the claimed invention. Even if one were motivated to combine Lerner with Sommers, Herrick-Davis and Barak, Applicants submit that the proposed combination would not yield the claimed invention because Lerner is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 1, 4, 5, 8, 10, 19-24, 26 and 29-32 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat, et al. (hereinafter "Dahiyat"). As discussed above, Herrick-Davis discloses that mutation of amino acid 312 from serine to phenylalanine or lysine in the serotonin 5-HT_2c receptor activates the receptor. The library is expressed in a mammalian host cell. However, according to the Examiner, Herrick-Davis does "not teach providing a library of coding sequences for potentially activating mutations of the candidate receptor protein and do not teach measuring the receptor activation with an indicator gene, which is modified by manipulation or replacement of the promoter sequence at the natural locus of the indicator gene and which is regulated by the receptor or ion channel in the host cell by using a heterologous reporter gene." (Office Action dated December 15, 2004, page 8). Further, Herrick-Davis specifically states that "the increases in agonist binding affinity and potency at the mutant receptors did not result from increased receptor expression but are *directly related to the substitutions*

made at amino acid no. 312." (Herrick-Davis, page 1141, col. 1, lines 1-5, emphasis added). Further, "[a]dditional studies were performed to determine if agonists other than 5-HT display an increased affinity for S312K receptors." (Herrick-Davis, page 1140, col. 2, first paragraph). Herrick-Davis does not disclose, nor even suggest substitution of amino acids other than no. 312.

The disclosure of Dahiyat does not cure the above-described deficiencies in Herrick-Davis for teaching or suggesting the claimed invention. Dahiyat allegedly discloses a method of designing a protein library for the substitution of residues in any part of a protein, and that a protein sequence can be designed through a fully automated sequence selection process to accomplish a library of a protein having various changes in the amino acids. While Dahiyat discloses that the automated sequence selection is an unbiased way of selecting amino acids for protein structure and function, and that it is not limited to a particular motif or folding sequences, Dahiyat does not limit the mutations to replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Dahiyat with Herrick-Davis to arrive at the claimed invention. Even if one were motivated to combine Dahiyat with Herrick-Davis, Applicants submit that the proposed combination would not yield the claimed invention because Dahiyat is absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claim 28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Herrick-Davis in view of Dahiyat and King, and further in view of Lerner. Applicants respectfully submit that the remarks above with regard to the differences between Herrick-Davis in view of Dahiyat apply equally here. The Examiner relies upon King for disclosing that reconstruction of a heterologous reporter system using the β-galactosidase gene (lacZ) in yeast would elucidate understanding of a ligand binding to the G protein coupled receptor and its activation. However, King does not disclose providing a library of coding sequences for potentially activating mutations of a candidate receptor or ion channel, which library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for

large side-chain amino acids, as required by the current invention. King further does not disclose expression of a library of mutant alleles in mammalian host cells to determine activation of a receptor by the mutants.

As discussed above, Lerner is concerned with identifying new drugs through expression in pigment cells. Lerner is absolutely silent with regard to use of a library of site directed mutations, wherein the library is generated by replacing coding sequences for small or medium side-chain amino acids with coding sequences for large side-chain amino acids, as required by the current invention. Accordingly, there is no suggestion to, and thus no expectation of successfully combining the disclosure of Lerner with Herrick-Davis, Dahiyat and King to arrive at the claimed invention. Even if one were motivated to combine Lerner with Herrick-Davis, Dahiyat and King, Applicants submit that the proposed combination would not yield the claimed invention because both Lerner and King are absolutely silent with regard to site directed mutations in a receptor or ion channel.

For the reasons provided above, Applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that *prima facie* obviousness of the invention over the cited references, either alone or in combination, has not been shown by the Examiner. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 for alleged lack of patentability are respectfully requested.

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 4, 5, 8-23 and 26-32 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Applicants submit check number 581834 in the total amount of $1,190.00 is enclosed as payment for the Request for Continued Examination (RCE) fee ($395.00) and the 4-month Petition for Extension of Time fee ($795.00). No other fee is deemed necessary in connection with this submission. However, the Commissioner is hereby authorized to charge any fees required by this submission, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number. A duplicate copy of this Transmittal Sheet is enclosed.

Respectfully submitted,

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